

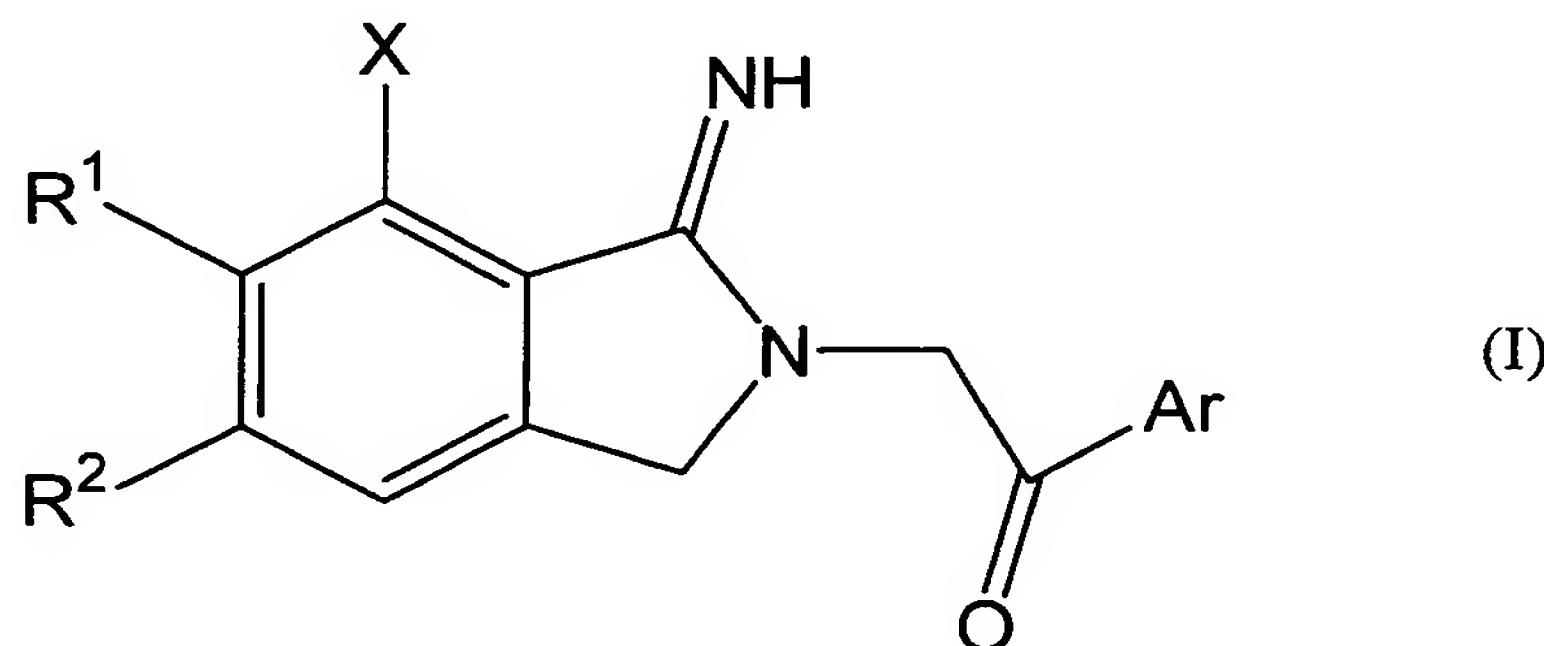
COMPOSITION CONTAINING BENZAMIDINE DERIVATIVE AND METHOD FOR  
STABILIZING BENZAMIDINE DERIVATIVE

## Technical Field

5 The present invention relates to a composition containing a benzamidine derivative and a method for stabilizing a benzamidine derivative.

## Background Art

The benzamidine derivative represented by the following general formula (I) 10 is a compound that has an antagonistic action on a thrombin receptor and is expected to provide an excellent effect in the treatment and prophylaxis of diseases with which thrombin is associated, such as, thrombosis, vascular restenosis, cerebral infarction, cardiac disease, disseminated intravascular coagulation syndrome, hypertension, inflammatory disease, rheumatism, asthma, glomerular nephritis, 15 osteoporosis, nervous disease, malignant tumor and the like (for example, see Patent Reference 1).



Patent Reference1 : International Publication WO 02 / 085855

### Problem to be Solved by the Invention

Although the benzamidine derivative represented by the general formula (I) or a pharmacologically acceptable salt thereof is a highly stable compound on its own, due to the coexistence with a formulation additive under humidification/heating 5 conditions in a solid state, and due to a high pH state in a liquid state, a decomposition product is sometimes generated by a reaction as shown in Fig. 1. A method has been devised, which enforces moisture proof packaging, as a method to increase the stability of the benzamidine derivative or the pharmacologically acceptable salt thereof; however, in this case, there is a problem of leading to an 10 increase in the manufacturing costs.

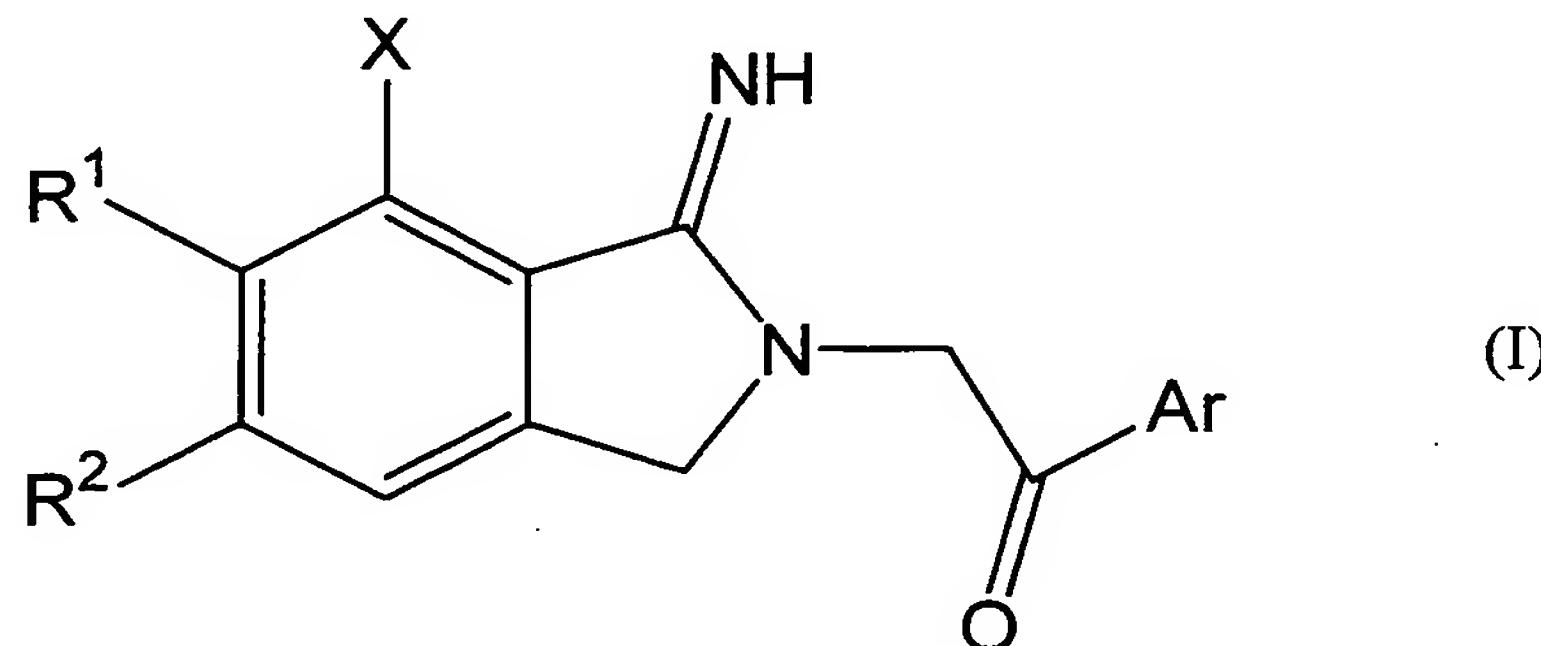
### Means for Solving the Problem

In view of the above, the present inventors, as a result of earnest study into solving the problems, reached completion of the present invention with the surprising 15 observation that by adding to a benzamidine derivative represented by chemical formula (I), at least one type of electrolyte selected from the group consisting of halide salts of alkaline metal or alkaline earth metal and alkaline metal salts or alkaline earth metal salts of perchloric acid, the benzamidine derivative could be stabilized. An object of the present invention is to provide a composition containing 20 a benzamidine derivative wherein decomposition does not occur readily even when placed under humidification / heating conditions and a method for stabilizing a benzamidine derivative. That is to say, a composition according to the present invention relates to:

(1) a composition comprising:

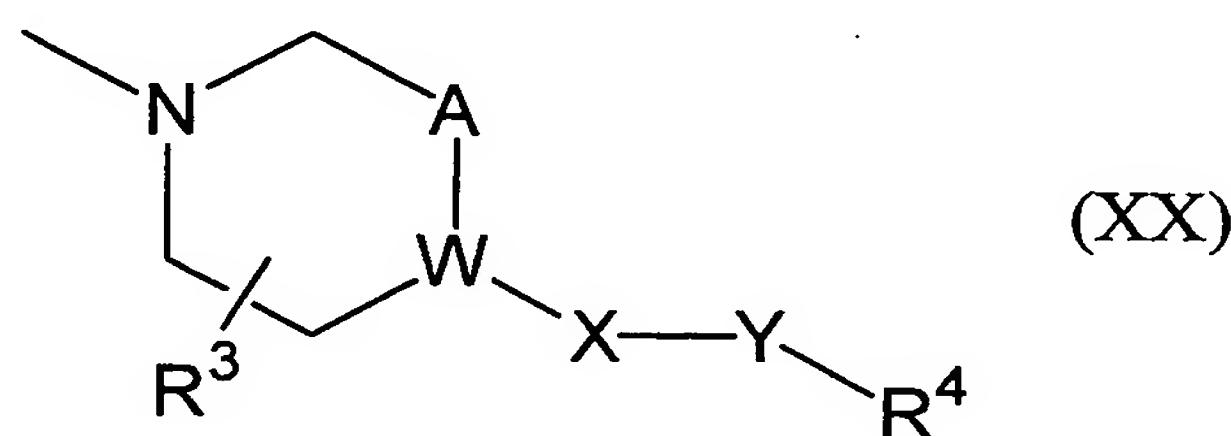
25 a benzamidine derivative represented by the following formula (I) or a pharmacologically acceptable salt thereof; and

at least one type of electrolyte selected from the group consisting of halide salts of alkaline metal or alkaline earth metal and alkaline metal salts or alkaline earth metal salts of perchloric acid:



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[wherein R<sup>1</sup> and R<sup>2</sup> are the same as or different from each other and each represents a hydrogen atom, a methoxy group or an ethoxy group, X represents a hydrogen atom or a halogen atom, and Ar represents a phenyl group that may be substituted with one or not less than two substituents selected from the group consisting of a methyl group, an ethyl group, a methoxy group, an ethoxy group, a *t*-butyl group, a morpholinyl group, or a substituent represented by the following formula (XX),



10 15 wherein W represents CH or a nitrogen atom, A represents CH<sub>2</sub> or a single bond, R<sup>3</sup> represents a hydrogen atom or OR<sup>5</sup>, X represents CH<sub>2</sub>, an oxygen atom, a single bond or a carbonyl group, Y represents a single bond or a C<sub>1-4</sub> alkyl group, R<sup>4</sup> represents a hydrogen atom, OR<sup>6</sup>, a cyano group or COOR<sup>7</sup>, and R<sup>5</sup>, R<sup>6</sup> and R<sup>7</sup> represent a hydrogen atom or a C<sub>1-4</sub> alkyl group.],

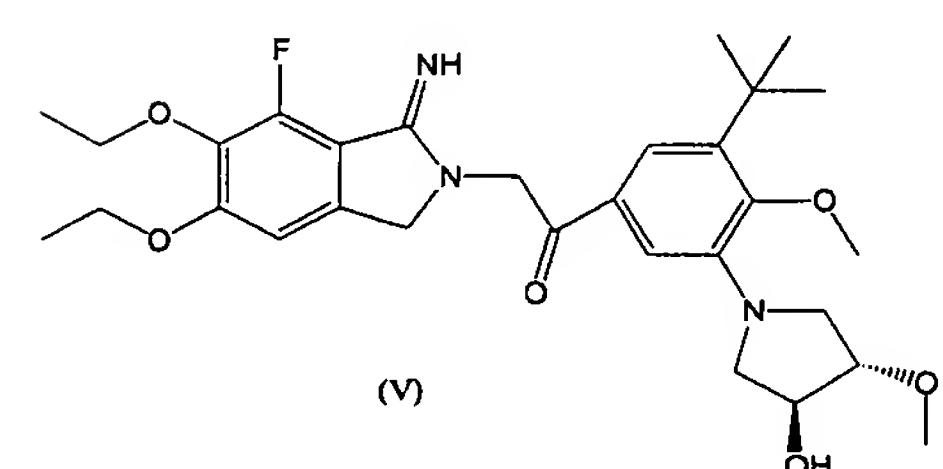
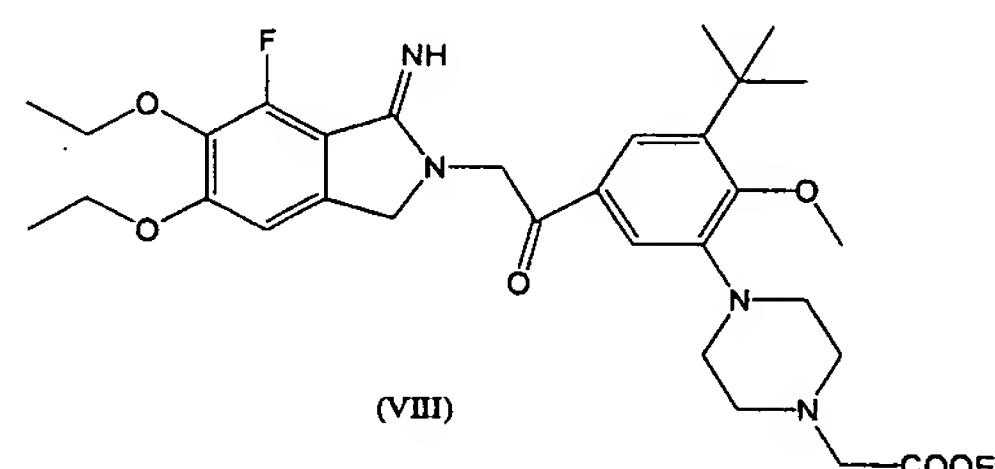
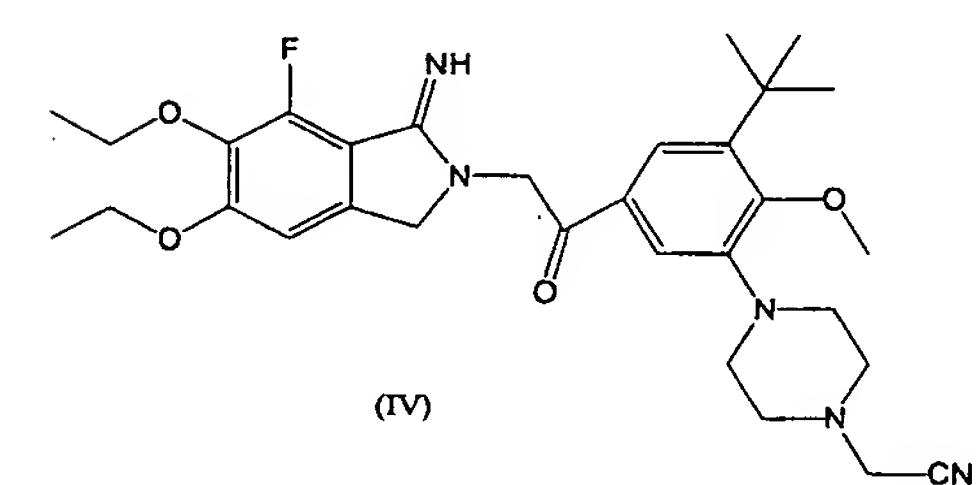
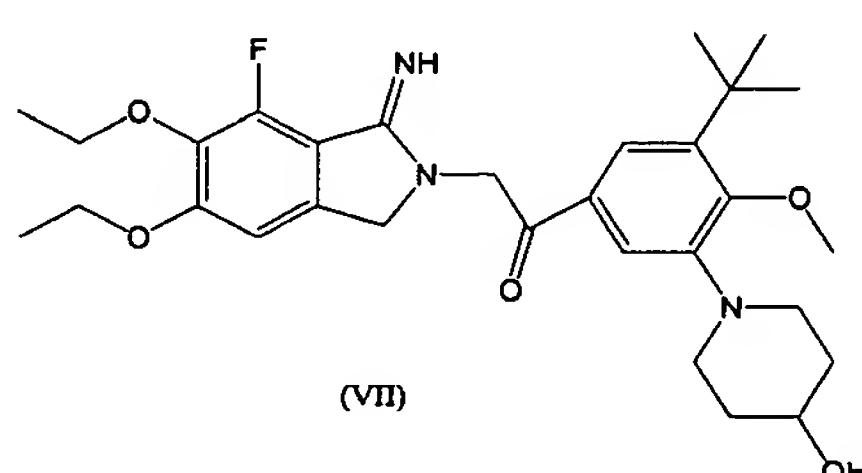
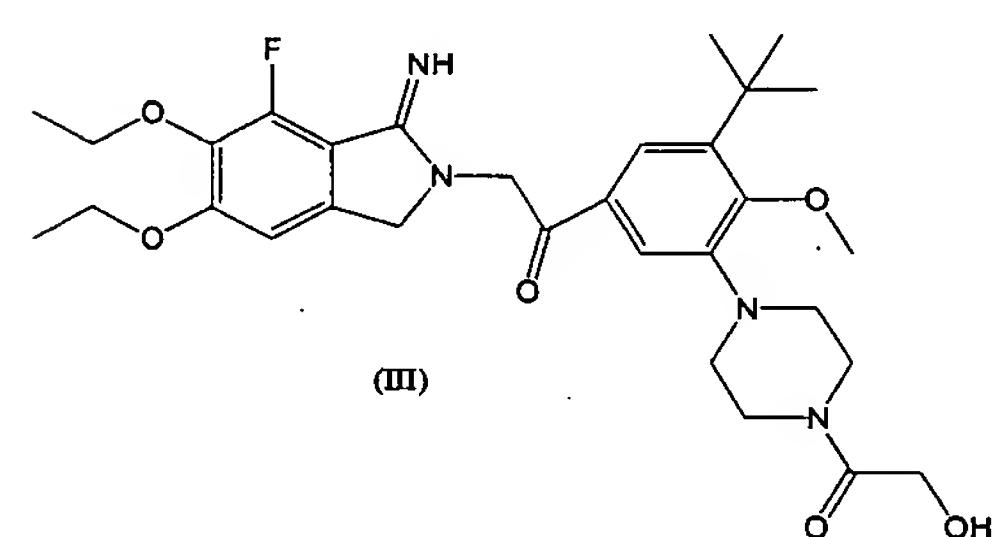
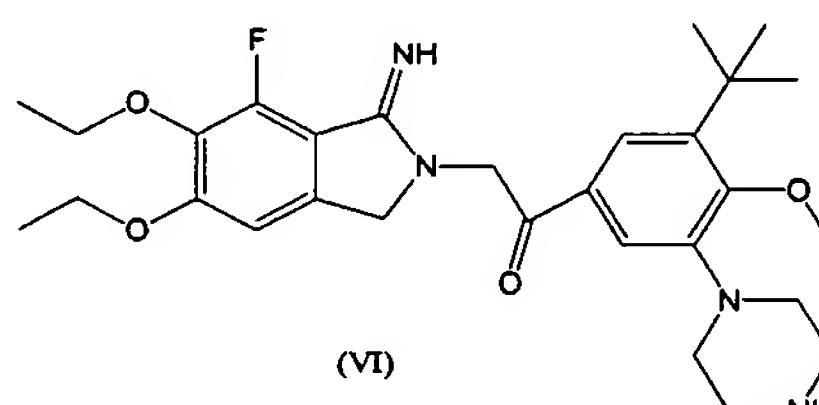
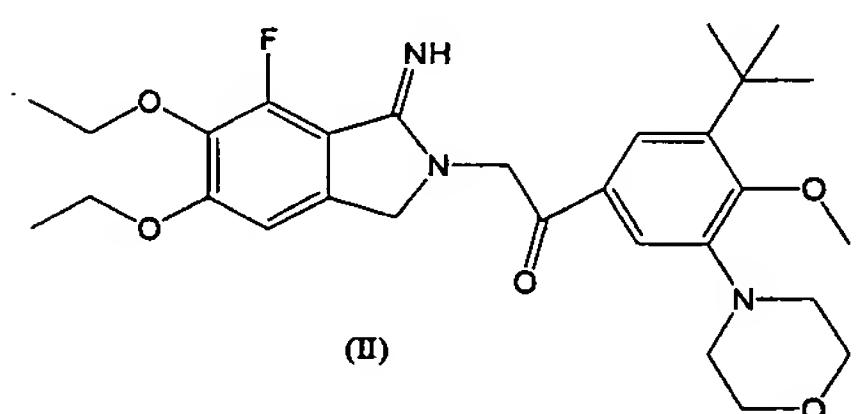
(2) the composition according to item (1), wherein the R<sup>1</sup> and R<sup>2</sup> represent an ethoxy group, and the X represents a fluorine atom,

(3) a composition comprising:

a benzamidine derivative represented by any one of the chemical formulae

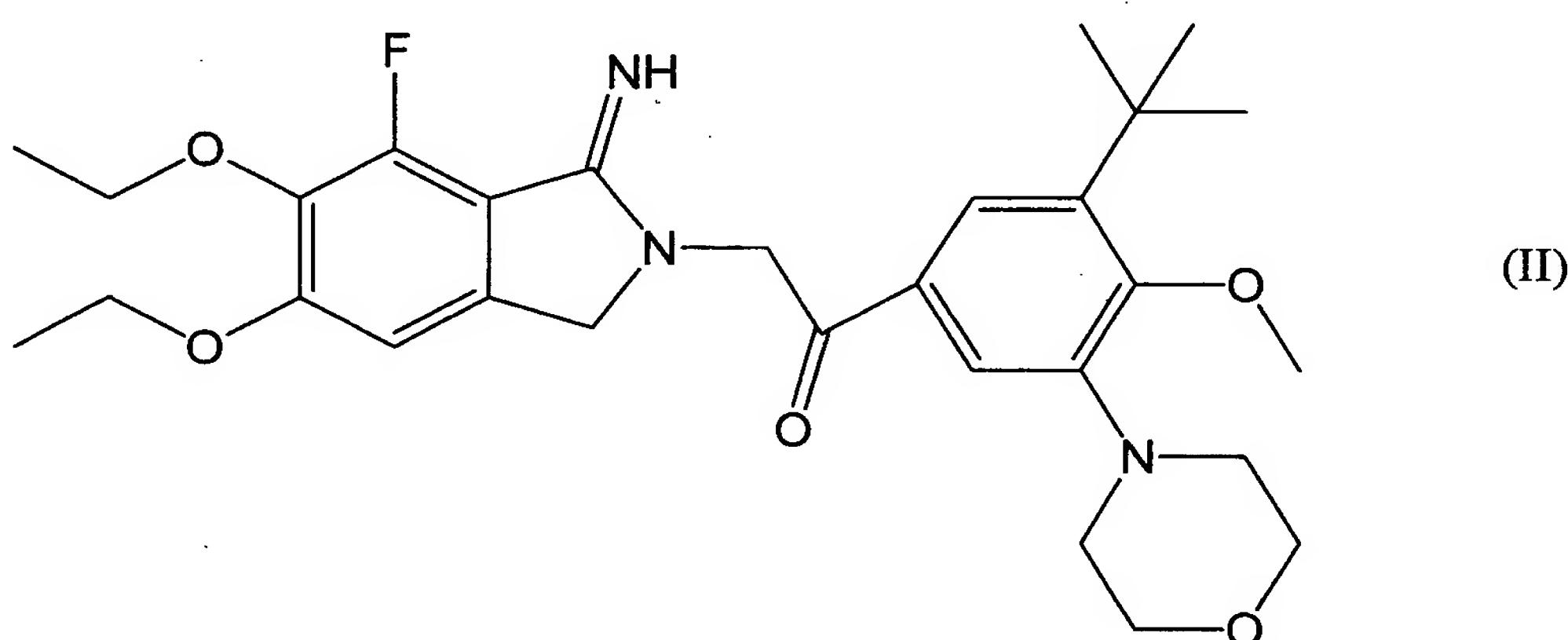
5 (II) to (VIII) or a pharmacologically acceptable salt thereof; and

at least one type of electrolyte selected from the group consisting of halide salts of alkaline metal or alkaline earth metal and alkaline metal salts or alkaline earth metal salts of perchloric acid:



(4) the composition according to any one of items (1) to (3), wherein an amount of the electrolyte based on one part by weight of the benzamidine derivative or the pharmacologically acceptable salt thereof is from 0.5 parts by weight to 30 parts by weight.

5 (5) the composition according to item (3), wherein the benzamidine derivative or  
the pharmacologically acceptable salt thereof is a hydrobromic acid salt of the  
benzamidine derivative represented by the following chemical formula (II):



In addition, a method for stabilizing a benzamidine derivative of the present

10 invention relates to:

(6) a method for stabilizing a benzamidine derivative, comprising the step of:  
adding to a benzamidine derivative represented by the chemical formula (I)

or a pharmacologically acceptable salt thereof, at least one type of electrolyte selected from the group consisting of halide salts of alkaline metal or alkaline earth metal and alkaline metal salts or alkaline earth metal salts of perchloric acid.

15 metal and alkaline metal salts or alkaline earth metal salts of perchloric acid,

(7) a method for stabilizing a benzamidine derivative, comprising the step of:  
adding to a benzamidine derivative represented by the chemical formula (II)-  
or a pharmacologically acceptable salt thereof, at least one type of electrolyte  
selected from the group consisting of halide salts of alkali metal or alkaline earth  
metal and alkali metal salts or alkaline earth metal salts of perchloric acid:

(8) the method according to item (6) or (7), wherein an amount of the electrolyte based on one part by weight of the benzamidine derivative is from 0.5 parts by weight to 30 parts by weight, and the like.

5    **Advantageous Effect of Invention**

The composition containing benzamidine derivative and the method for stabilizing the composition containing the benzamidine derivative according to the present invention has the following advantageous effects. That is to say, the composition of the benzamidine derivative with excellent stability can be formulated 10 in order to prevent decomposition reaction from occurring under humidification conditions; in addition, as moisture proof packaging is not needed, the manufacturing costs can be lowered.

Brief Description of Drawing(s)

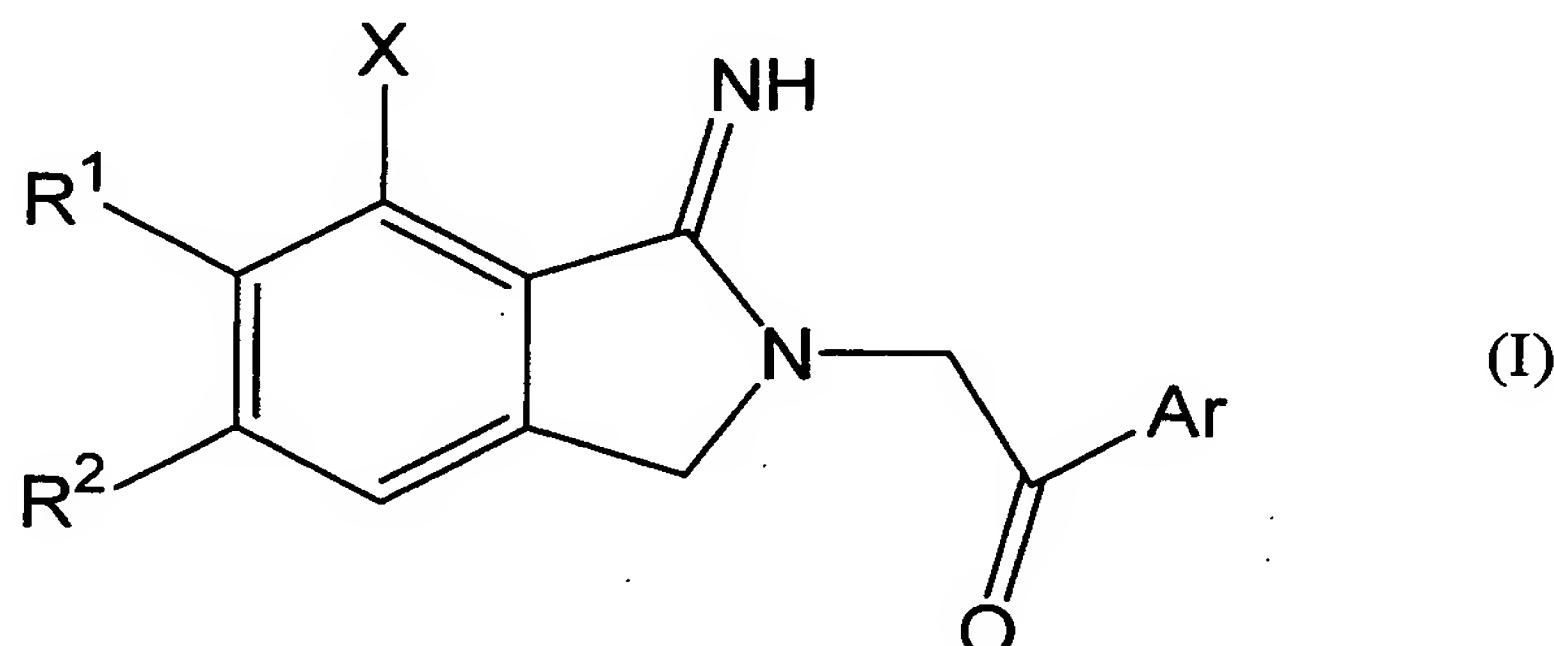
15    Fig. 1 illustrates decomposition of a benzamidine derivative.

**Best Mode for Carrying Out the Invention**

The embodiment is an example to describe the present invention, and is not intended to limit the present invention solely to this embodiment. The present 20 invention can be carried out in various forms, as long as they do not depart from the spirit thereof.

The composition according to the present invention comprises (1) a benzamidine derivative or a pharmacologically acceptable salt thereof and (2) at least one type of electrolyte selected from the group consisting of halide salts of 25 alkaline metal or alkaline earth metal and alkaline metal salts or alkaline earth metal salts of perchloric acid.

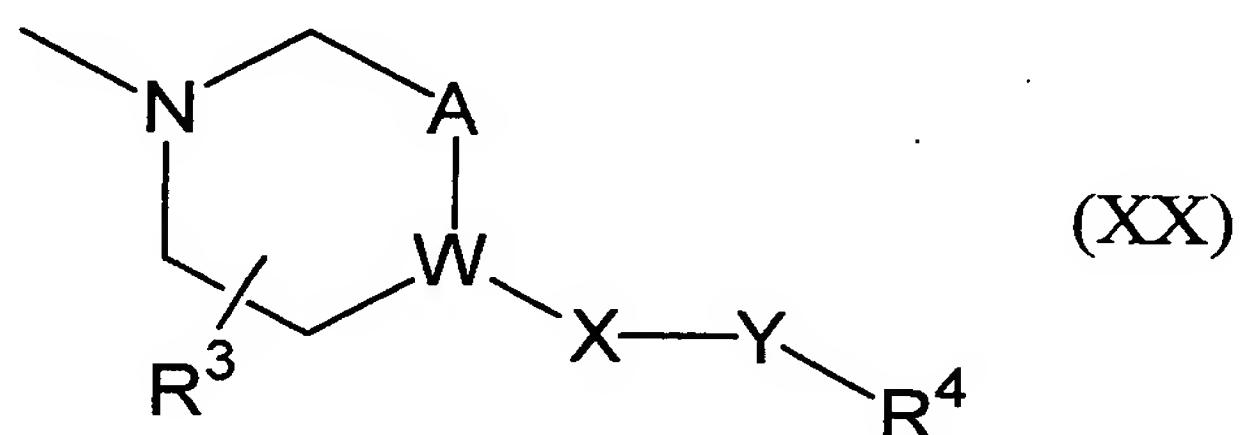
The benzamidine derivative used in the present invention can be synthesized by the method described in, for example, International Publication WO 02 / 085855, and the examples of the benzamidine derivative include benzamidine compound represented by chemical formula (I).



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[wherein R<sup>1</sup> and R<sup>2</sup> are the same as or different from each other, and each represents a hydrogen atom, a methoxy group or an ethoxy group, X represents a hydrogen atom or a halogen atom, and Ar represents a phenyl group that may be substituted with one or not less than two substituents selected from the group consisting of a methyl group, an ethyl group, a methoxy group, an ethoxy group, a *t*-butyl group, a morpholinyl group, or a substituent represented by the following formula (XX),

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wherein W represents CH or a nitrogen atom, A represents CH<sub>2</sub> or a single bond, R<sup>3</sup> represents a hydrogen atom or OR<sup>5</sup>, X represents CH<sub>2</sub>, an oxygen atom, a single bond or a carbonyl group, Y represents a single bond or a C<sub>1-4</sub> alkyl group, R<sup>4</sup> represents a hydrogen atom, OR<sup>6</sup>, a cyano group or COOR<sup>7</sup>, R<sup>5</sup>, R<sup>6</sup> and R<sup>7</sup>

represent a hydrogen atom or a C<sub>1-4</sub> alkyl group.].

The term "halogen atom" used in the present invention means a fluorine atom, a chlorine atom, a bromine atom, an iodide atom and the like, preferably the fluorine atom or the chlorine atom, and more preferably the fluorine atom. The term 5 "C<sub>1-4</sub> alkyl group" used in the present invention means a linear or branched alkyl group having 1 to 4 carbons, and examples of "C<sub>1-4</sub> alkyl group" include a methyl group, an ethyl group, a *n*-propyl group, an *iso*-propyl group, a *n*-butyl group, a *iso*-butyl group, a *sec*-butyl group, a *tert*-butyl group and the like.

The use of compounds A to G shown in Table 1 may be preferred as the 10 benzimidine compound represented in chemical formula (I) used the present invention, and their respective names are as follows:

A: 1-(3-*tert*-butyl-4-methoxy-5-morpholinophenyl)-2-(5,6-diethoxy-7-fluoro-1-imino-1,3-dihydroisoindol-2-yl)ethanone,

B: 1-{3-*tert*-butyl-5-[4-(2-hydroxyacetyl)piperazin-1-yl]4-methoxyphenyl}-2-(5,6-diethoxy-7-fluoro-1-imino-1,3-dihydroisoindol-2-yl)ethanone,

C: (4-{3-*tert*-butyl-5-[2-(5,6-diethoxy-7-fluoro-1-imino-1,3-dihydroisoindol-2-yl)acetyl]-2-methoxyphenyl)piperazin-1-yl)acetonitrile,

D: 1-{3-*tert*-butyl-5-[(3S,4S)-3-hydroxy-4-methoxypyrrolidin-1-yl]-4-methoxyphenyl}-2-(5,6-diethoxy-7-fluoro-1-imino-1,3-dihydroisoindol-2-yl)ethanone,

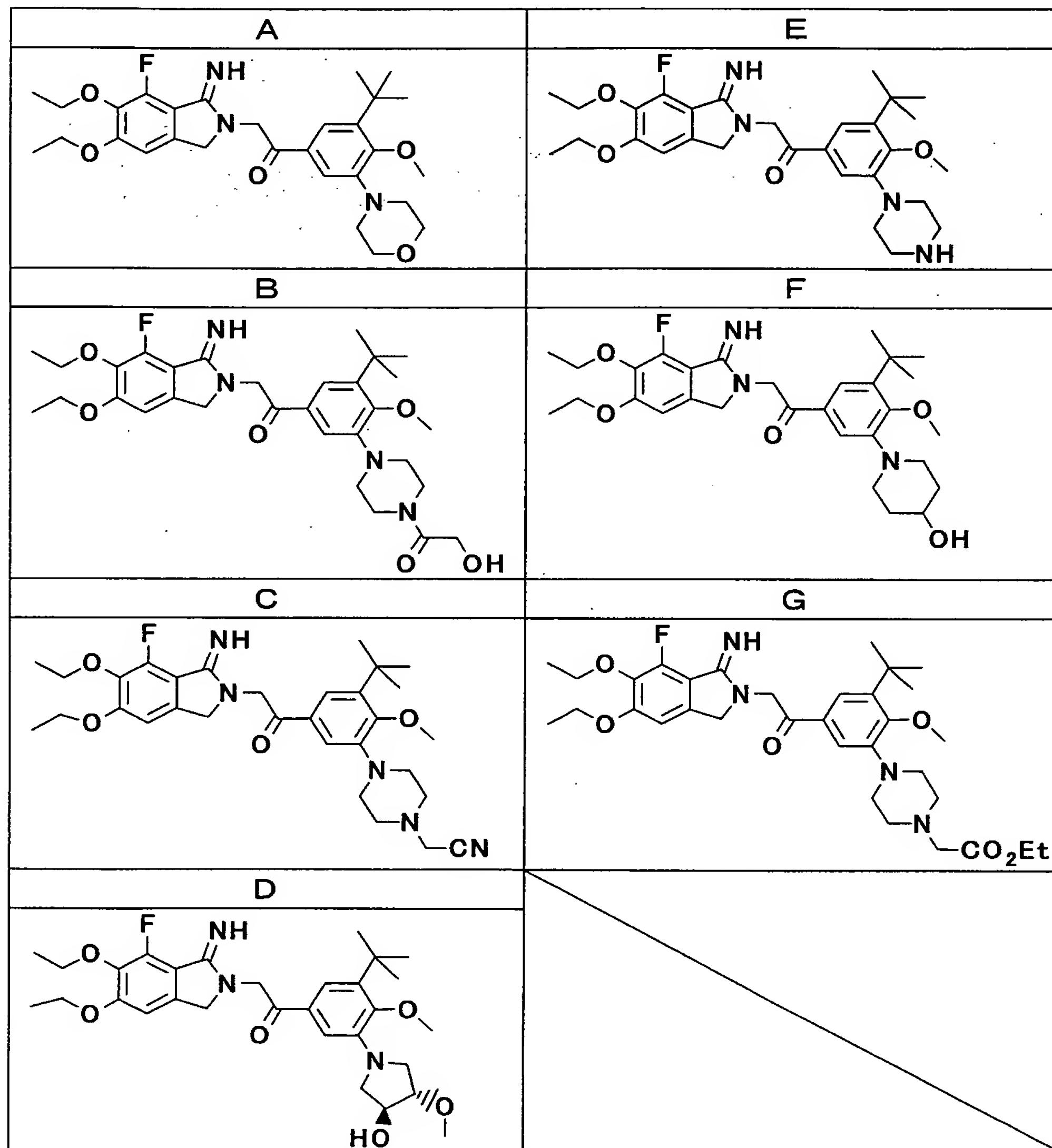
E: 1-(3-*tert*-butyl-4-methoxy-5-piperazin-1-ylphenyl)-2-(5,6-diethoxy-7-fluoro-1-imino-1,3-dihydroisoindol-2-yl)ethanone,

F: 1-[3-*tert*-butyl-5-(4-hydroxypiperidin-1-yl)-4-methoxyphenyl]-2-(5,6-diethoxy-7-fluoro-1-imino-1,3-dihydroisoindol-2-yl)ethanone,

G: ethyl (4-{3-*tert*-butyl-5-[2-(5,6-diethoxy-7-fluoro-1-imino-1,3-dihydroisoindol-2-yl)-2-methoxyphenyl)piperazin-1-yl)acetate.

Among these, the use of 1-(3-*tert*-butyl-4-methoxy-5-morpholinophenyl)-2-(5,6-diethoxy-7-fluoro-1-imino-1,3-dihydroisoindol-2-yl)ethanone (compound A in Table 1) is particularly preferred, in which case, the use of the hydrobromic acid salt thereof is preferred.

5 Table 1



10 The benzamidine derivative used in the present invention may be a free form or a pharmacologically acceptable salt thereof. Herein, there is no limitation to a "pharmacologically acceptable salt" used in the present invention, as long as it forms a salt with the compound according to the present invention and is pharmacologically

acceptable; preferred examples include hydrohalic acid salts (for example, hydrochloric acid salt, hydrobromic acid salt, hydroiodic acid salt and the like), inorganic acid salts (for example, sulfate, nitrate, perchlorate, phosphate, carbonate, bicarbonate and the like), organic carboxylates (for example, acetate, maleate, 5 tartrate, fumarate, citrate and the like), organic sulfonates (for example, methanesulfonate, ethanesulfonate, benzenesulfonate, toluenesulfonate, camphor sulfonate and the like), amino acids (for example, aspartate, glutamate and the like), quaternary ammonium salts, alkaline metal salts (for example, sodium salt, potassium salt and the like), alkaline earth metal salts (for example, magnesium salt, 10 calcium salt and the like), and the like; among which, the use of hydrobromic acid salt is the most preferable.

Any salt containing a halide ion or a perchlorate ion may be used as the electrolyte used in the present invention, for example, the use of a halide salt of an alkaline metal or an alkaline earth metal or an alkaline metal salt or an alkaline earth 15 metal salt of perchloric acid is preferred. More specifically, the use of NaCl, KCl, MgCl<sub>2</sub>, CaCl<sub>2</sub>, KBr, or KI is preferred.

There is no particular limitation on an amount of electrolyte used in the present invention, which can be adjusted according to the type and amount of benzamidine derivative, the dosage form of the preparation, the type of the 20 electrolyte, and the like. Based on one part by weight of the benzamidine derivative, the amount of electrolyte is generally from 0.5 to 30 parts by weight, preferably from 1 to 20 parts by weight and more preferably from 1.5 to 7.5 parts by weight.

There is no particular limitation in the dosage form when formulating the composition containing the benzamidine derivative according to the present 25 invention, which can be made in any dosage form, for example, tablets, granules, powders, fine granules and the like. Additive generally used in a formulation step,

such as diluents, binders, coating agents, colorants, flavorants and the like may also be included during formulation.

There is no particular limitation on the one-time dose of the benzamidine derivative used in the present invention, which can be adjusted according to the 5 dosage form, disease, symptom, age, body weight, sex and the like. The one-time dose is generally from 0.1mg to 500mg, preferably from 0.5mg to 200mg, and more preferably from 1mg to 100mg.

The present invention also provides a method for stabilizing the benzamidine derivative comprising the step of adding to the benzamidine derivative represented 10 by the chemical formula (I) or pharmacologically acceptable salt thereof, at least one type of electrolyte selected from the group consisting of halide salts of alkaline metal or alkaline earth metal and alkaline metal salts or alkaline earth metal salts of perchloric acid.

The present invention will be described in further detail with the following test 15 examples and examples; however the scope of the present invention is not limited to these. Based on the description of the present invention, a variety of changes and modifications are possible by those skilled in the art, and these changes and modifications are also included in the present invention.

20 (Tablet Stability Test)

A preparation stability test of the composition containing a benzamidine derivative according to the present invention was carried out. The tablet stability test was carried out by analyzing with HPLC amounts of decomposition product (degradant) in tablets obtained in Example 1 and Example 2, which have been 25 stored at 60°C and 75% relative humidity (60°C / 75% R.H.) for one week, and comparing with the reference group, which has been stored in cold. The test result

of the tablet containing 1mg of compound A is shown in Table 2, and the test result of the tablet containing 10mg is shown in Table 3.

[Table 2]

1mg T Storage for 1W	Without NaCl		With NaCl	
	Water content (%)	Degradant (%)	Water content (%)	Degradant (%)
Cold Storage	0.43	0.16	0.84	0.13
60°C / 75 % R.H.	1.27	11.34	5.19	2.85

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[Table 3]

10mgT storage for 1W	Without NaCl		With NaCl	
	Water content (%)	Degradant (%)	Water content (%)	Degradant (%)
Cold Storage	0.10	0.09	0.77	0.08
60°C / 75 % R.H.	0.89	1.30	6.46	0.73

As can be apparent from Tables 2 and 3, under heating / humidification conditions, in both the 1mg tablet and the 10mg tablet of the composition containing a benzamidine derivative according to the present invention, the increase in the amount of impurity was inhibited, as compared to the composition in which NaCl was not added.

#### (Granule Stability Test)

Next, the results of the granule stability test of the composition containing the benzamidine derivative according to the present invention are shown. In the present test, the amount of decomposition product after storing granules obtained in Examples 3 to 7 at 60°C for 42 hours in 75% relative humidity was compared with that of the reference group. The results are shown in Table 4.

[Table 4]

60°C/75%RH open for 42hrs

Ex	Sample	degradant(%)
-	Reference	2.41
3	NaCl	1.49
4	KCl	1.74
5	KBr	1.09
6	KI	1.07
7	NaClO <sub>4</sub>	1.01

As can be apparent from Table 4, in all the granules of the composition containing the benzamidine derivative according to the present invention, the amount of decomposition product is less, as compared to the reference in which no electrolyte was added, and the stabilization effect due to the addition of the electrolyte was confirmed.

## (Lyophilized Powder Stability Test)

The results of a lyophilized powder stability test of the composition containing a benzamidine derivative according to the present invention is shown in the following. In the present test, the amount of decomposition product after storing lyophilized powders obtained in Examples 8 to 23 for 60 hours at 60°C and 75% relative humidity was compared with that of the reference group. The results are shown in Table 5.

[Table 5]

Example	Compound	Electrolyte	Decomposition product (%)	Example	Compound	Electrolyte	Decomposition product (%)
Reference	B	-	14.4	Reference	E	-	22.6
8		NaClO <sub>4</sub>	6.0	16		NaCl	22.0
9		KBr	10.6	17		NaClO <sub>4</sub>	8.3
Reference	C	-	13.4	18	E	KBr	14.4
10		NaClO <sub>4</sub>	<7	19		NaCl	8.5
11		KBr	<7	20		NaClO <sub>4</sub>	5.8
Reference	D	-	12.0	21	E	KBr	14.5
12		NaClO <sub>4</sub>	5.8	Reference		-	25.6
13		KBr	8.6	22		NaClO <sub>4</sub>	10.5
Reference	F	-	9.5	23	G	KBr	17.7
14		NaClO <sub>4</sub>	4.6				
15		KBr	6.9				

As can be apparent from Table 5, due to the addition of the electrolyte, the amount of decomposition product was less in all the benzamidine derivatives, as compared to the reference where no electrolyte was added, and the stabilization effect due to the addition of the electrolyte was confirmed.

(Example)

In the following, as examples of compositions containing the benzamidine derivative according to the present invention, specific examples using compounds listed in Table 1 will be shown; however, the scope of the patent is not limited to these.

(Example 1)

According to the following procedure, a tablet containing compound A was

prepared.

(1) Into a 1L mixer were added 1g of compound A, 117g of lactose (manufactured by DMV Japan), 7.5g of low-substituted hydroxypropyl cellulose (sometimes abbreviated simply as "L-HPC"; manufactured by Shin-Etsu Chemical) and 4.5g of

5 hydroxypropylmethyl cellulose (sometimes abbreviated simply as "HPMC"; manufactured by Shin-Etsu Chemical), which were mixed by stirring.

(2) Then, while stirring, a suitable amount of purified water in which 4.5g of NaCl (Manufactured by Wako Pure Chemical) was dissolved was added for granulation.

(3) The granulated granule was dried at 60°C for 5 hours in a dryer.

10 (4) To this were added 15g of crystalline cellulose (manufactured by Asahi Kasei Chemicals) and 0.75g of magnesium stearate (Manufactured by Mallinckrodt), which were then mixed in a vinyl bag.

(5) The powder was tableted with a single punch tabletting machine, so as to obtain a tablet containing 1mg of compound A in one tablet (150mg) with a tablet diameter of 6.5mm.

#### (Example 2)

Changing the amount of compound A added, a tablet containing 10mg of compound A in one tablet (150mg) was obtained by an approximately identical 20 procedure to Example 1.

#### (Example 3)

(1) Into a mixer (tablet grinder) were added 0.25g of compound A, 27g of lactose (Manufactured by DMV Japan), 1.5g of low-substituted hydroxypropyl cellulose (manufactured by Shin-Etsu Chemical) and 0.9g of HPMC (manufactured by Shin-Etsu Chemical), which were mixed by stirring.

(2) Weighing 940mg of the powder prepared in (1) and 64mg of NaCl (Manufactured by Wako Pure Chemical), a mortar was used for mixing, then, a suitable amount of purified water was added for granulation.

(3) The granulated granule was dried at 60°C for 5 hours in a dryer, to obtain a

5 granule containing compound A and NaCl.

(Examples 4 to 7)

Using each of KCl, KBr, KI and NaClO<sub>4</sub> instead of NaCl as an electrolyte, granules containing compound A were obtained in a similar procedure to Example 3.

10

(Example 8)

According to the following procedure, a lyophilized powder containing compound B was prepared.

(1) Over a microplate fitted with a filter were added dropwise 0.05ml of a methanol water solution (volume ratio was MeOH:H<sub>2</sub>O = 3:7) containing 0.05mg of compound B, 0.05ml of water suspension containing 4mg of Placebo component (component ratio: lactose / L-HPC / HPMC = 92 / 5 / 3), and 0.025ml aqueous solution containing 0.252mg of NaClO<sub>4</sub>.

(2) After stirring with a plate mixer, the plate was frozen in a freezer at -40°C for 3 hours.

(3) Lyophilization was carried out for approximately 24 hours to obtain a lyophilized powder on the microplate.

(Example 9)

25 Using KBr instead of NaClO<sub>4</sub> as electrolyte, a lyophilized powder containing 0.05mg of compound B, 4mg of Placebo component, and 0.21mg of KBr was

obtained by a similar procedure to Example 8.

(Examples 10 to 23)

Lyophilized powders containing compounds C to G were prepared by a similar procedure to Example 8. The amounts of electrolyte added in the lyophilized powders obtained in Examples 8 to 23 are grouped in Table 6. In addition, for each compound, a lyophilized powder containing no electrolyte was prepared as a reference by preparing according to a similar procedure to Example 8.

10 [Table 6]

Example	Compound	Electrolyte	Amount added (mg)	Example	Compound	Electrolyte	Amount added (mg)
8	B	NaClO <sub>4</sub>	0.252	16	E	NaCl	0.105
9		KBr	0.210	17		NaClO <sub>4</sub>	0.252
10	C	NaClO <sub>4</sub>	0.252	18		KBr	0.210
11		KBr	0.210	19		NaCl	0.210
12	D	NaClO <sub>4</sub>	0.252	20		NaClO <sub>4</sub>	0.504
13		KBr	0.210	21		KBr	0.420
14	F	NaClO <sub>4</sub>	0.252	22	G	NaClO <sub>4</sub>	0.252
15		KBr	0.210	23		KBr	0.210

#### Industrial Applicability

The composition containing the benzamidine derivative and the method for stabilizing the composition containing the benzamidine derivative according to the present invention have the following effects: A preparation of the benzamidine derivative with excellent stability can be realized in order to prevent decomposition reaction from occurring under humidification conditions; in addition, as moisture proof packaging is not needed, thereby the manufacturing costs can be lowered.